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Eberhardt, Christina ; Schwarzwald, Colin C

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Quantification of left atrial contractile function using two-dimensional speckle tracking echocardiography in horses after conversion of atrial fibrillation to sinus rhythm☆

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KEYWORDS
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Transvenous electrical cardioversion

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Results: Global S_L and SR_L, as well as active LA fractional area change (FAC) identified cases with LA dysfunction after TVEC and QS cardioversion and proved useful to demonstrate LA functional recovery over time. Agreement between active LA

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FAC and S_L and SR_L, respectively, to diagnose atrial dysfunction was substantial to fair at 24 h after cardioversion and decreased with time.

Conclusion: This study shows that 2DST is useful to quantify LA contractile dysfunction in horses after cardioversion of AF.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in horses affecting performance. In the equine athlete, AF commonly exists in the absence of any clinically relevant underlying structural cardiac disease, although microstructural lesions or channelopathies predisposing to AF might be present in some of these horses [1]. Once sustained, AF itself causes time-dependent electrical, functional, and structural remodeling within the atria, which favor perpetuation of the arrhythmia [2,3]. Pre-existing microstructural alterations and AF-induced myocardial remodeling within the atria may hamper cardioversion of sustained AF to normal sinus rhythm (NSR) and can cause atrial contractile dysfunction, termed atrial stunning, after successful cardioversion [4,5]. Recovery of left atrial (LA) contractile function and reverse remodeling after cardioversion may take days to several weeks until full function is regained. Persistent atrial dysfunction indicates irreversible atrial remodeling and might represent a poor prognostic sign [2].

Abbreviations

2D	two-dimensional
2DE	two-dimensional echocardiography
2DST	two-dimensional speckle tracking
AF	atrial fibrillation
BWT	body weight
CI	confidence interval
ECG	electrocardiogram
FAC	fractional area change
HR	heart rate or heart rates
hr	hours
κ	kappa
LA	left atrium or left atrial
LAA	left atrial area
LAD	left atrial diameter
NSR	normal sinus rhythm
QS	Quinidine sulfate
S_L	longitudinal strain
SR_L	longitudinal strain rate
TVEC	Transvenous electrical cardioversion

Follow-up echocardiographic examinations are useful to monitor atrial contractile function within the first days and weeks after cardioversion [4,6]. The methods for assessment of LA mechanical function using two-dimensional echocardiography (2DE) and tissue Doppler imaging have been described [4,7–9] and decreased active LA fractional area change (FAC) at 24 h (hr) after cardioversion was shown to predict recurrence of AF [10]. However, the most accurate, reliable, and clinically most useful methods to assess atrial contractile dysfunction and the risk of recurrent AF after cardioversion are yet to be determined.

Two-dimensional speckle tracking (2DST) echocardiography has been shown to be a feasible and reliable quantitative ultrasound technique for assessment of LA mechanical function in healthy people [11–13]. In healthy horses, 2DST has been used to characterize systolic radial, circumferential, and longitudinal motion of the left and right ventricle [9,14–16]. Furthermore, 2DST has been applied to assess ventricular function in horses with myocardial disease [17–19]. Recently, we showed that 2DST-based LA wall motion analysis is a feasible and reliable method for quantification of global mechanical LA function and we reported reference intervals for LA global longitudinal strain (S_L) and strain rate (SR_L) in healthy Warmblood horses [20].

Two-dimensional speckle tracking-derived LA S_L has been demonstrated to be a useful index in diagnosis, prognostication and follow-up of AF in people [21] and several studies showed that LA S_L is a powerful predictor of recurrence of AF [22–24]. Therefore, 2DST might represent a promising supplemental technique to aid in the clinical assessment of LA function in horses with AF after successful cardioversion to NSR.

The aim of this study was to provide proof-of-concept for use of 2DST to detect compromised LA contractile function (booster pump function) in Warmblood horses after successful cardioversion of AF to NSR. We hypothesized that 2DST-derived global S_L and SR_L are commonly low at 24 h, indicating LA contractile dysfunction, and

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Q2

Table 1 General characteristics of the study sample.

	TVEC group	QS group
n	11	8 (10)[a]
Signalement		
Breed	Warmblood	Warmblood
Sex	7 male, 4 female	7 male, 1 female
Age (mean, range)	11.8 (7–24) years	12.6 (6–19) years
BWT (mean, range)	591 (485–730) kg	615 (540–700) kg
Duration of AF	<1 month (n = 2), 1–3 months (n = 3), >3 months (n = 3), unknown (n = 3)	<1 month (n = 7), 1–3 months (n = 1), unknown (n = 2)
Time in NSR	1–3 months (n = 3), 3 months to 1 year (n = 5), >1 year (n = 3)	<1 year (n = 1), >1 year (n = 8), unknown (n = 1)
Treatment	Number of shocks (median, range): 5 (1–14) Energy (median, range): 200 (100–360) Joule	Quinidine dose: 22 mg/kg PO q2h (max. 4 doses), then continued q6h Total dose (median, range): 77 (22–132) mg/kg
Supplementary treatment after cardioversion	Sotalol (n = 5), sotalol + quinapril (n = 4), none (n = 2)	Sotalol + quinapril (n = 1), quinapril (n = 2), none (n = 7)

AF, atrial fibrillation; BWT, body weight; n, number; NSR, normal sinus rhythm; PO, per os; QS, Quinidine sulfate; TVEC, transvenous electrical cardioversion.
[a] 10 QS conversions in 8 horses.

progressively increase within 72 h and 1–6 months after cardioversion.

Animals, material and methods

Study sample

The study sample comprised Warmblood horses that were diagnosed with AF and presented to the Clinic for Equine Internal Medicine of the Vetsuisse Faculty, University of Zurich, Switzerland between 2007 and 2019 for cardioversion. Characteristics of the study sample are summarized in Table 1.

Atrial fibrillation was diagnosed based on a surface electrocardiogram (ECG) recording. Standard two-dimensional (2D) and Doppler echocardiography served to rule out severe underlying structural cardiac disease before treatment. Horses included in this study were successfully treated by means of pharmacological quinidine sulfate (QS) cardioversion or transvenous electrical cardioversion (TVEC) and remained in sinus rhythm for at least 1 month after cardioversion. Complete echocardiographic examinations were performed in all horses at 24 h and 72 h after cardioversion. When possible, recheck examination including a surface ECG recording and a complete echocardiographic examination was performed between 1 and 6 months after cardioversion at the Clinic for Equine Internal Medicine of the Vetsuisse Faculty. Horses that did not present for recheck examination were followed-up on phone calls with referring veterinarians to confirm persistence of NSR; no follow-up ECG and echocardiogram was possible in these cases.

Echocardiography and 2DST analyses

Horses were unsedated but restrained by an experienced handler in a quiet room for the examination. Echocardiographic examinations were performed using a GE Vivid 7 echocardiograph with a M4S probe set at a frequency of 1.5/3.6 MHz (octave harmonics) or a GE Vivid e95 echocardiograph with a 4Vc-D probe operated in 2D mode and set at a frequency of 1.4/2.8 MHz[a]. The imaging depth was kept at 30 cm, and the sector width was reduced to achieve a recording frame rate of 50–60 frames/s in 2D mode. A single lead base-apex ECG was recorded simultaneously for timing purposes. A minimum of three representative recordings including three cardiac cycles each were recorded in each view and stored as cine-loops in digital raw data format for offline analyses. Start and end of the cardiac cycle were defined by the QRS complex. Cycles immediately after a premature beat, a sinus pause, or a 2nd degree atrioventricular block were precluded from analyses.

[a] GE Healthcare, Glattbrugg, Switzerland.

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Routine transthoracic 2D, M-mode, color Doppler and tissue Doppler echocardiography were performed according to a standardized protocol to assess cardiac structures, valvular competence, chamber dimensions, and left ventricular systolic and diastolic function by use of standard right and left-parasternal long-axis and short-axis views [9]. The LA was imaged in right and left-parasternal four-chamber views, optimized to obtain an image of the entire atrium at its maximal dimensions.

Previously described echocardiographic variables were measured to characterize LA size and function [4,7–9]. Dimensional measurements included: Internal LA diameter measured at the widest distance parallel to the mitral valve annulus at the time of maximum atrial filling (i.e. one frame before mitral valve opening; LAD_{max}), internal LA area measured at maximum atrial filling (LAA_{max}), at the onset of active atrial contraction (i.e. at the onset of the electrocardiographic P wave; LAA_a), and at minimum atrial filling (i.e. at the time of closure of the mitral valve; LAA_{min}) on a right-parasternal four-chamber view optimized to image the entire LA; internal area of the LA during maximum atrial filling (i.e. one frame after the closure of the aortic valve) on a right-parasternal short-axis view of the LA and the aorta ($LAA_{sx\text{-}max}$); LA diameter measured at the widest distance during maximum atrial filling on a left-parasternal long-axis view optimized to image the LA ($LAD_{llx\text{-}max}$). These measurements were corrected for differences in body weight (BWT) using the following equations: diameter (500) $=$ measured diameter$/BWT^{1/3} \times 500^{1/3}$; area (500) $=$ measured area$/BWT^{2/3} \times 500^{2/3}$. The active FAC of the LA was calculated as: active LA FAC (%) $= (LAA_a - LAA_{min})/LAA_a \times 100$.

Two-dimensional speckle tracking analysis was performed offline on the digitally stored cine-loop recordings of the LA using the 'Q-Analysis' module of the EchoPAC software[b] as described previously [20]. The 2DST analyses were performed on the appropriate right-parasternal long-axis view focusing on the LA. The start and the end of the cardiac cycle was defined by the onset of the P wave (P wave trigger) on the simultaneously recorded ECG. Global S_L and global SR_L were measured during the period of active LA contraction (booster pump phase), as the distance from zero baseline to the first most negative S_L and SR_L peak, respectively, just before mitral valve closure (Fig. 1). All measurements were made in triplicates (measurement of three non-consecutive cycles) and averages were used for further analyses.

Data analysis and statistics

All statistical and graphical analyses were performed by standard computer software[c]. To detect the effect of treatment modality (TVEC and QS) and time point (24 h, 72 h and recheck examination) on heart rate (HR), on 2DE-derived indices of LA size and function and on 2DST-derived measurements for LA booster pump function (global S_L and global SR_L), a two-way mixed-model ANOVA with Holm-Sidak post hoc test was performed. Homogeneity of variances was assessed by graphical display of the data and validity of the normality assumption was confirmed by assessment of normal probability plots of the residuals.

To assess the association between global S_L and global SR_L, respectively, and 2DE-derived indices of LA size and function, multiple linear regression was performed; repeated measures over time in the same horse and treatment effects were accounted for using dummy variables (effects coding). Appropriateness of the linear model was assessed by graphical display of the data and assessment of normal probability plots of the residuals.

Cohen's kappa statistics were performed using GraphPad QuickCalcs[d] to quantify agreement of global S_L and SR_L, respectively, with LA active FAC on the diagnosis of atrial dysfunction at the three different time points (24 h, 72 h and recheck examination) after cardioversion; for this purpose, atrial dysfunction was defined as a value below the reference intervals described for LA active FAC [8], S_L, and SR_L [20]. Thereby, κ was interpreted as follows: 0.81–1.0, almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; 0.01–0.20, slight agreement; 0, no agreement [25]. The overall significance level was defined as $p < 0.05$.

Results

Eleven successful transvenous electrical cardioversions (TVEC group) were performed in 11 Warmblood horses and ten successful

[b] Echopac, version 201, GE Healthcare, Glattbrugg, Switzerland.

[c] SigmaPlot 12.3, Systat Software Inc., San Jose, California, USA.

[d] GraphPad Software, Online calculator, www.graphpad.com/quickcalcs, San Diego, California, USA.

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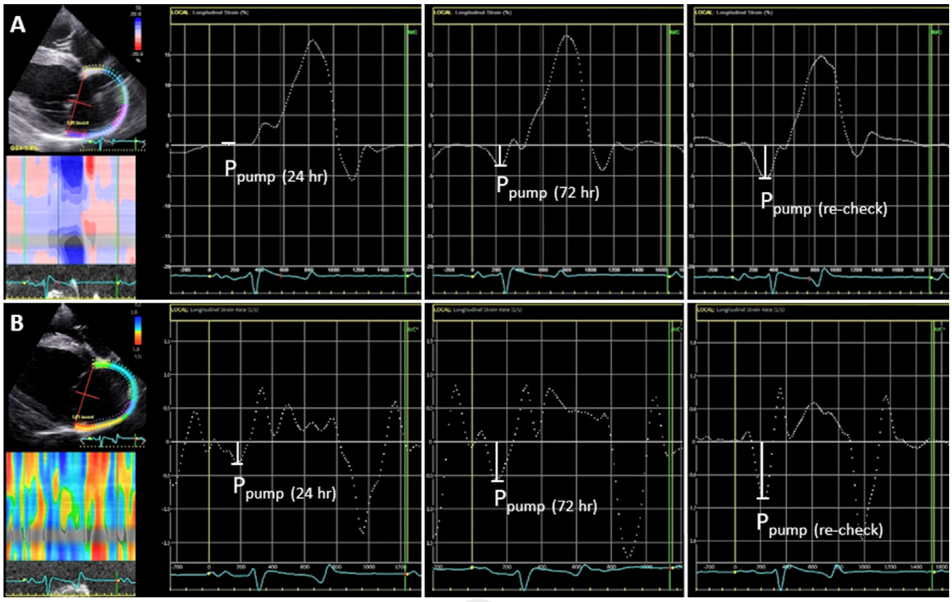

Figure 1 Two-dimensional speckle tracking analysis of the left atrium (LA). Representative trace screens of (A) global longitudinal strain (S_L) and (B) global longitudinal strain rate (SR_L) throughout the cardiac cycle are shown. Top left, two-dimensional image with the segmented region of interest and parametric color coding; Bottom left, color M-mode with parametric color coding; Right, dotted lines represent global S_L (A) and global SR_L (B) at three different time points (24 h (hr), 72 h and 1–6 months re-check) in the same horse. An electrocardiogram is plotted for timing purposes. The yellow line marks the onset of the P wave (P wave trigger). P_{pump}: Global S_L and global SR_L during LA mechanical function (booster pump function) measured as the distance from zero baseline to the first most negative peak, respectively, just before mitral valve closure.

pharmacological cardioversions with QS (QS group) were performed in eight Warmblood horses. One horse had three successful QS cardioversions performed because of two recurrences of AF; for the purpose of this proof-of-concept study, these were counted as individual cases.

Echocardiographic data were available for all 21 cases at 24 h and 72 h after cardioversion, and for 16 cases that were presented to the clinic for a recheck examination at 1 month (13 cases), 2 months (one case), 4 months (one case), and 6 months (one case) after cardioversion. Four cases were followed-up by phone call with the referring veterinarians to ensure that they were still in NSR 1 month after cardioversion, and one case was lost for follow-up.

The HR ranged between 28 and 49/min in all horses at all time points. No significant differences were detected between the TVEC group and the QS group ($p = 0.578$; difference of means [95% confidence interval (CI)]: −1 [-3 to +2]/min). However, the HR decreased significantly between 24 h and 72 h after cardioversion ($p < 0.001$; −5 [-2 to −7]/min) and between 24 h after cardioversion and the recheck examination ($p < 0.001$; −7 [-4 to −9]/min); no significant difference was detected between 72 h after cardioversion and the recheck examination ($p = 0.164$; −2 [1 to −5/min]).

Conventional LA area and diameter measurements of the study sample after cardioversion are summarized in Fig. 2. Most horses had normal or enlarged LA dimensions 24 h after cardioversion. No significant differences were detected between the TVEC group and the QS group at any time point. A significant difference between time points, independent of treatment group, was only detected for $LAA_{sx\text{-}max}$ between 72 h and the recheck examination after cardioversion.

Indices of LA function are summarized in Fig. 3. Based on active LA FAC, nine out of 11 cases in the TVEC group and seven out of ten cases in the QS group were diagnosed with atrial mechanical dysfunction at 24 h after cardioversion (Fig. 3A). No significant differences between treatment groups were detected at any time point. Independent of treatment group, significant increase in active LA FAC was detected over time.

Based on global S_L, atrial contractile dysfunction at 24 h after cardioversion was diagnosed in nine out of 11 horses in the TVEC group and four out of ten horses in the QS group (Fig. 3B). Significant differences between treatment groups were not detected at any time point. Global S_L increased significantly (i.e. became more negative) over time, with all cases within the reference range at the recheck examination.

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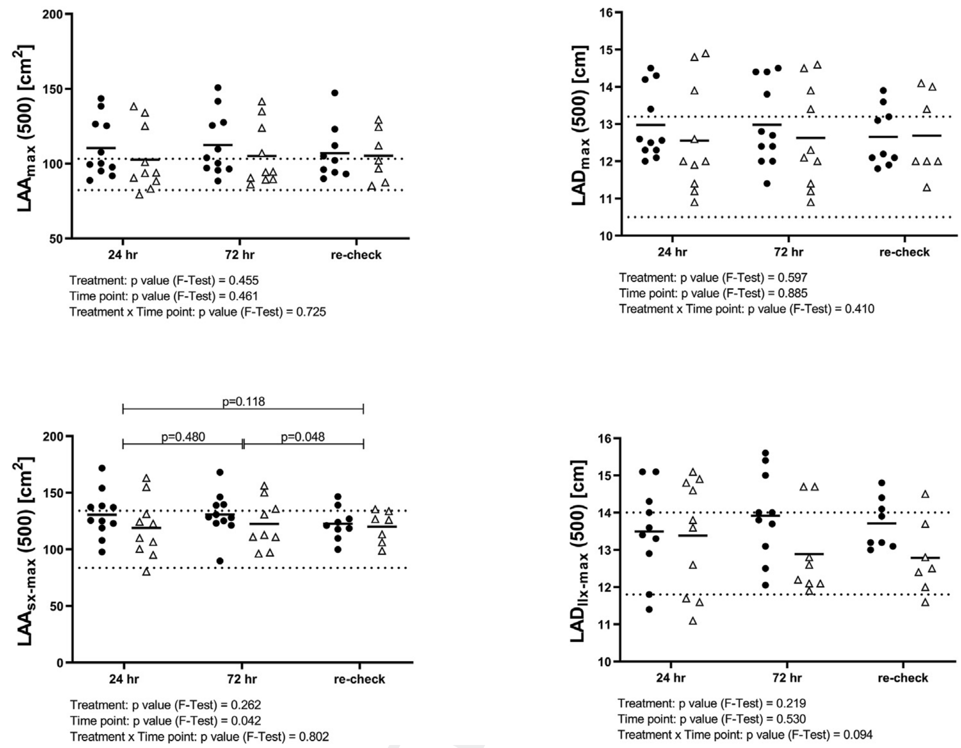


Fig.1 2 Scatter dot plot of conventional two-dimensional echocardiography derived variables of left atrial (LA) size for the two treatment groups (transvenous electrical cardioversion, solid circles; quinidine sulfate, open triangles) at three different time points (24 h (hr), 72 h and 1–6 months recheck) after successful cardioversion. The dotted lines represent the upper and lower level of the reference interval [8]. Mean values are indicated by horizontal lines. Data points represent single measurements. LAA$_{max}$: Internal LA area measured during maximum atrial filling on a right-parasternal long-axis view; LAA$_{sx-max}$: Internal area of the LA during maximum atrial filling on a right-parasternal short-axis view; LAD$_{llx-max}$: LA diameter measured at the widest distance during maximum atrial filling on a left-parasternal long-axis view; LAD$_{max}$: Internal LA diameter measured at the widest distance parallel to the mitral valve annulus during maximum atrial filling in the same view. All measurements were scaled to a body weight of 500 kg.

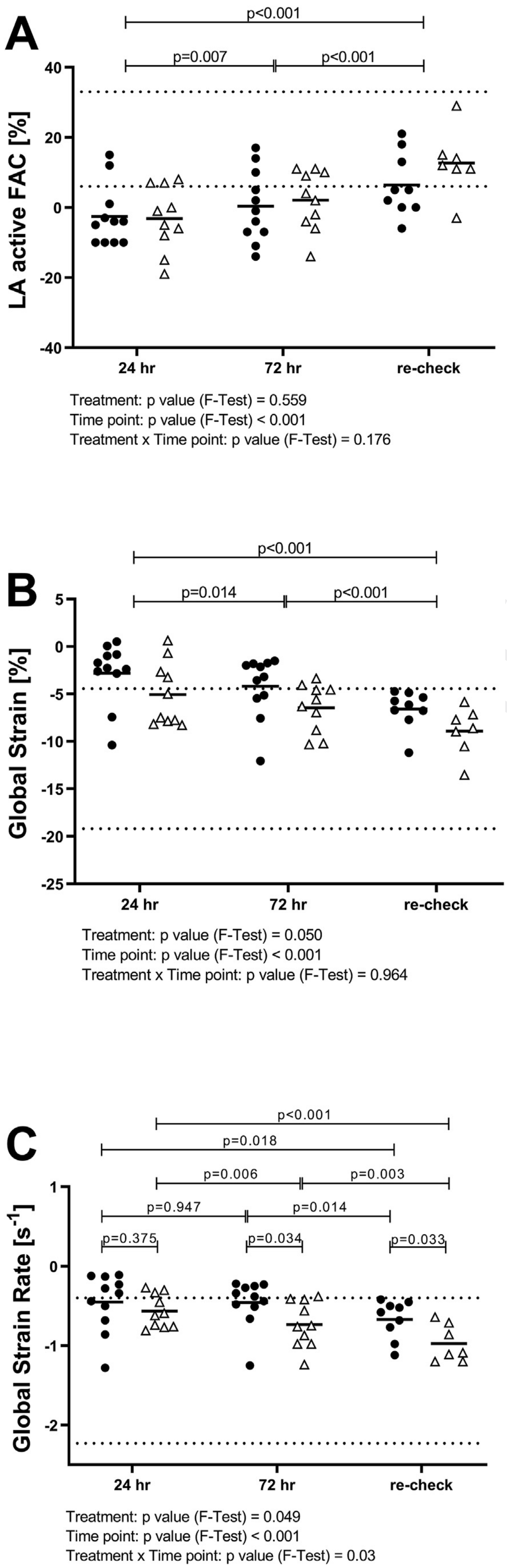
Global longitudinal strain rate identified six out of 11 cases in the TVEC group and three out of ten cases in the QS group with atrial contractile dysfunction at 24 h after cardioversion (Fig. 3C). There was no significant difference at 24 h after cardioversion between treatment groups, but at 72 h after cardioversion and at the recheck examination SR$_L$ was significantly lower (i.e. less negative) in the TVEC group compared to the QS group. Increase in SR$_L$ (i.e. becoming more negative) within the TVEC group was significant between 24 h and the recheck examination, as well as 72 h and the recheck examination but not between 24 h and 72 h. A significant increase in SR$_L$ within the QS group was detected between all time points. Based on global SR$_L$, all horses had low-normal atrial function at time of recheck examination.

Multiple linear regression analyses revealed that global S$_L$ and SR$_L$ were significantly associated with active LA FAC (Table 2) but not to any of the indices of LA size.

Agreement between global S$_L$ and active LA FAC for the diagnosis of atrial dysfunction was substantial at 24 h after cardioversion ($\kappa = 0.674$; 95% CI, 0.350 to 0.997), fair at 72 h after cardioversion ($\kappa = 0.364$; 95% CI: 0.018 to 0.710), and absent at time of recheck examination ($\kappa = 0.000$; 95% CI: -0.000 to 0.000). Agreement between global SR$_L$ and active LA FAC was fair at 24 h ($\kappa = 0.323$; 95% CI: 0.051 to 0.594) and 72 h after cardioversion ($\kappa = 0.364$; 95% CI: 0.018 to 0.710) and slight at time of recheck examination ($\kappa = 0.177$; 95% CI: -0.144 to 0.499) (Fig. 4).

Discussion

The results of this study show that 2DST echocardiography is a feasible technique to assess LA contractile function in horses with AF after cardioversion to NSR. Furthermore, this study



confirms previous findings of reverse functional remodeling and shows that in addition to active LA FAC, global S_L and SR_L are useful variables to diagnose atrial dysfunction after cardioversion of AF and detect recovery thereof over time.

Two-dimensional echocardiographic indices of atrial mechanical function have previously been described in horses [7,8] and active LA FAC has been used in several studies to detect atrial dysfunction in horses after cardioversion of AF to NSR over time [4–6]. However, 2DE-derived active LA FAC is not a direct measurement of LA function but rather represents a calculated index from two static LA area measurements. Those indices represent 2D measurements of a complex three-dimensional structure which do not necessarily reflect true atrial size. In the literature, there is no consensus regarding the indices used to calculate active LA FAC. While in the present study, active LA FAC was calculated from LAA_a (area at onset of active atrial contraction, e.g. onset of P wave) and LAA_{min} (area at mitral valve closure) as described previously [4,7,8]; others have used a different definition for LAA_{min}, namely subjectively smallest LA area at maximal active atrial contraction [10]. This measurement possesses a potentially greater measurement variability, as the frame of minimal atrial area has to be selected subjectively. Furthermore, in cases with marked atrial stunning (i.e., severely diminished or absent atrial contraction) the definition of this measurement precludes accurate measurement. Measurement of LAA_{min} at mitral valve closure is clearly defined, reducing measurement variability. However, it may not represent true minimal LA dimension as mitral valve closure is associated with LA relaxation. Furthermore, 2DE-derived variables of LA mechanical function, including active LA FAC, were shown to have moderate intraobserver and interobserver within- and between days variability [7]. Analysis of myocardial wall motion is a useful technique for assessment of myocardial function.

Fig. 3 Scatter dot plot of conventional two-dimensional echocardiography derived active left atrial fractional area change (active LA FAC) and two-dimensional speckle tracking (2DST) derived global longitudinal strain and strain rate for the two treatment groups (transvenous electrical cardioversion, solid circles; quinidine sulfate, open triangles) at three different time points (24 h (hr), 72 h and 1–6 months recheck) after successful cardioversion. The dotted lines represent the upper and lower level of the reference interval [8,20]. Mean values are indicated by horizontal lines. Data points represent single measurements. For detailed explanation of 2DST-derived variables see Fig. 1.

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Table 2 Multiple linear regression analyses. Association between global longitudinal strain and longitudinal strain rate and two-dimensional echocardiography derived indices of left atrial size and function.

	Global longitudinal strain (S_L)				Global longitudinal strain rate (SR_L)			
	n	R^2	Adj R^2	p	n	R^2	Adj R^2	p
LAD_{max} (500)	58	0.668	0.474	0.429	58	0.772	0.639	0.605
LAA_{max} (500)	58	0.662	0.465	0.891	58	0.771	0.637	0.820
$LAA_{sx\text{-}max}$ (500)	57	0.688	0.501	0.111	57	0.792	0.668	0.068
$LAD_{llx\text{-}max}$ (500)	53	0.647	0.426	0.907	53	0.766	0.619	0.550
Active LA FAC	58	0.834	0.737	<0.001	58	0.893	0.830	<0.001

Active LA FAC, active left atrial fractional area change; Adj R^2, adjusted R square; LA, left atrium or left atrial; $LAA_{max,}$ maximum LA area in right-parasternal long-axis view; $LAA_{sx\text{-}max,}$ maximum LA area in right-parasternal short-axis view; $LAD_{llx\text{-}max,}$ maximum LA diameter in left-parasternal long-axis view; $LAD_{max,}$ maximum LA diameter in right-parasternal long-axis view; $S_{L,}$ longitudinal strain; $SR_{L,}$ longitudinal strain rate; (500), allometrically scaled to a body weight of 500 kg.

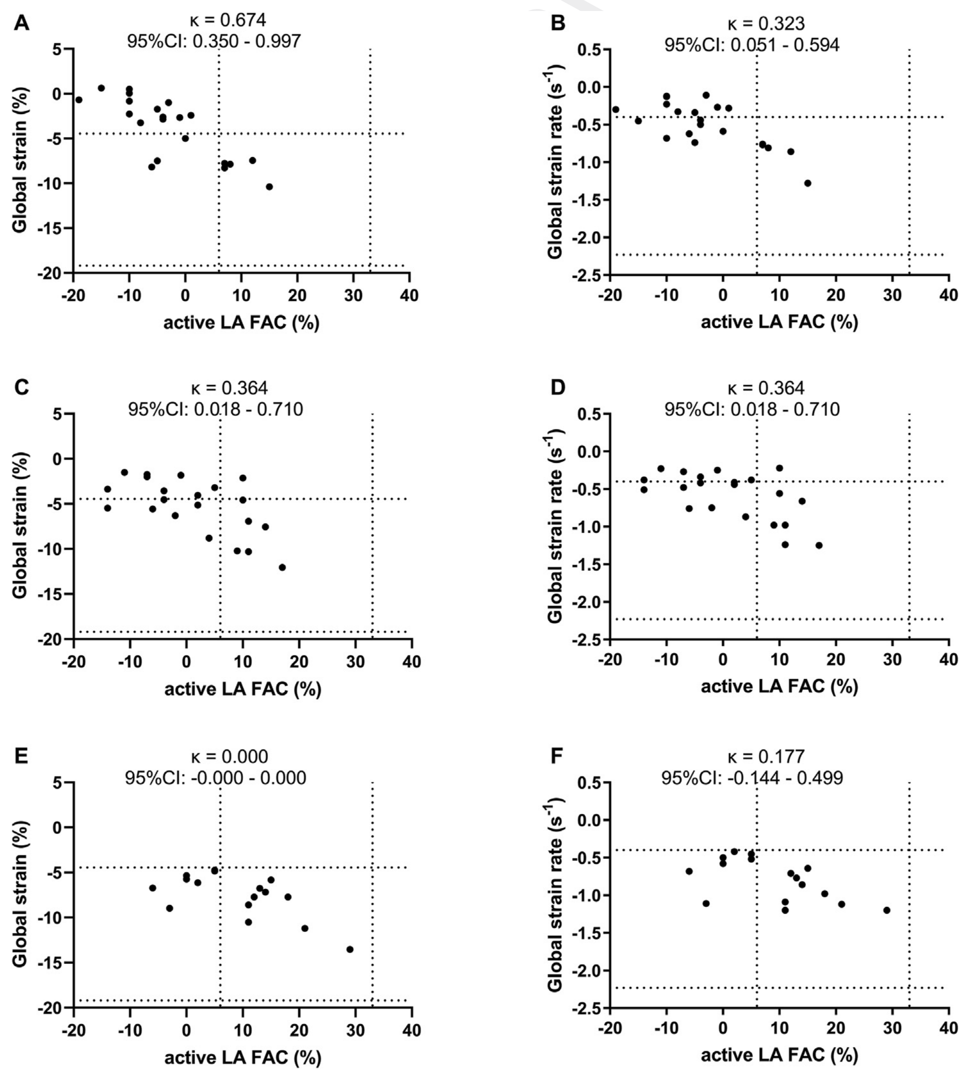

Fig. 4 Method agreement for active left atrial fractional area change (LA FAC) with global longitudinal strain (S_L, left panel) and global longitudinal strain rate (SR_L, right panel) to diagnose atrial dysfunction at three different time points (A and B: 24 h (hr); C and D: 72 h; E and F: 1–6 months re-check). The dots represent individual cases. The dotted lines represent the upper and lower limit of the reference intervals for the respective variable [8,20]. CI: Confidence interval; κ: Kappa. For detailed explanation of variables see Figs. 1 and 3.

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Two-dimensional speckle tracking echocardiography allows for objective and quantitative evaluation of segmental and global myocardial velocities, strain, and strain rate. It is angle-independent, does not require high recording frame rates, and is relatively independent of the 'tethering effect' compared with tissue Doppler imaging [26]. Tissue Doppler imaging measures focal wall motion velocity toward or away from the transducer and calculates strain and strain rate at this particular point in the myocardium [27]. As opposed to 2DST, it is highly angle dependent, influenced by translational motion, and does not easily allow quantitative assessment of segmental or global LA wall motion. In man, conventional echocardiographic indices proved reliable to assess LA function in a clinical setting, but 2DST-derived variables have now become widely used to assess atrial function in a variety of cardiac diseases [28–31]. Left atrial S_L, for example, has been demonstrated to be a useful complementary index in diagnosis, prognostication, and follow-up of AF in people [21].

Assessment of LA function by 2DST may also become a useful addition to conventional imaging techniques in veterinary medicine. Speckle tracking echocardiography of the LA was found to be useful in differentiating stages of myxomatous mitral valve disease in dogs [32,33] and atrial function was assessed by LA S_L in a canine model of chronic AF and heart failure [34]. Peak atrial longitudinal strain was found to be a univariate predictor of cardiac-related death in dogs with myxomatous mitral valve disease [35].

However, to date, there is no gold standard set of 2DST variables to describe LA mechanical function [36]. Left atrial strain and strain rate curve patterns differ based on the chosen trigger (P wave or R wave trigger), resulting in different 2DST measurements and normal reference values. The curve profile of the P wave trigger method with the corresponding peak variables more closely represents myocardial deformation from the atrial perspective and is the preferred method over the R wave trigger for 2DST analyses of the LA for subjects in sinus rhythm [37]. Recently, we reported the use of segmental and global measurements to quantify LA myocardial wall motion in healthy Warmblood horses using a P wave trigger. We found that global S_L and SR_L measurements have considerably lower intra- and interobserver measurement variability in comparison to segmental measurements [20]. Therefore, we concluded that global 2DST variables are more likely to be clinically applicable and may prove useful for assessment of LA mechanical function in horses with heart disease. Short- and long-term atrial dysfunction in horses after cardioversion have been demonstrated, and reverse remodeling after cardioversion may take a few days to several weeks depending on AF duration [4–6]. Because LA enlargement and atrial dysfunction in horses after cardioversion of AF are associated with increased risk of recurrence of AF [10,38]; and vigorous exercise and high atrial pressures and stretch are triggers for AF [39,40], the recommendations in regards to aftercare for successful cardioversion of AF, include short- and long-term echocardiographic follow-up examinations to monitor atrial recovery after cardioversion. Assessment of atrial function after cardioversion can aid in reducing the required resting period while allowing adequate time for reverse atrial remodeling [1,2]. However, the most accurate, reliable, and clinically most useful methods are yet to be determined.

In this study, echocardiographic examinations where performed at 24 h, 72 h and 1–6 months after cardioversion to test the performance of S_L and SR_L to diagnose atrial mechanical dysfunction and early recovery of atrial contractile function, and to follow-up horses with long-term atrial stunning. Similar time points had been used in previous studies to demonstrate short-term and long-term improvement of atrial function after cardioversion of AF by 2DE [4,6]. Atrial dysfunction 24 h after cardioversion was detected in 16 out of 21 horses by 2DE-derived active LA FAC, and in 13 of 21 and nine of 21 horses by 2DST-derived LA global S_L and SR_L, respectively. Active LA FAC was significantly associated with S_L and SR_L. Also, we found a substantial agreement between active LA FAC and global S_L, and a fair agreement between active LA FAC and global SR_L for diagnosis of atrial dysfunction 24 h after cardioversion. This finding confirms the hypothesis that 2DST-derived global S_L and SR_L are commonly low at 24 h, are therefore useful to detect LA contractile dysfunction, and can be used complementary to 2DE indices. Although, an overall short-term improvement of atrial function was detected, only few cases recovered to full extent by 72 h based on 2DE and 2DST variables. This is in line with other studies that indicate that most cases even with short duration of AF require several days for reverse remodeling [5].

While all cases were hospitalized for 3 days after cardioversion which allowed for the 24 h and 72 h examination, only 16 of 21 cases presented for their follow-up examination. The preferred follow-up time point in the authors' institution is 1 month, however three cases within the QS group could

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only be followed-up at later time points (2–6 months). While this represents a limitation in regard to analysis of long-term recovery of atrial function, for the purpose of this proof-of-concept study, one recheck examination group including all cases independent of exact time point was formed. A significant long-term improvement of atrial function was found by means of global S_L and SR_L, as well as active LA FAC. This finding shows that the course of atrial dysfunction and the recovery thereof can be tracked not only by 2DE but also by 2DST variables.

Agreement on the diagnosis of atrial dysfunction between 2DE and 2DST variables decreased with time point. While there was substantial to fair agreement in the short-term follow-up, agreement at the time of re-check examination was slight between active LA FAC and SR_L, and there was no agreement between active LA FAC and S_L. Based on S_L and SR_L, atrial function had normalized in all cases (i.e. measurements were within the reference range) at time of recheck examination, while seven cases where diagnosed with persistent atrial stunning based on active LA FAC. Another study that investigated long-term atrial function based on echocardiographic data found that most horses had normal atrial function 7 weeks after cardioversion [6].

For the purpose of this study, atrial dysfunction was defined as a value below the respective reference range [8,20]. Most cases diagnosed with atrial dysfunction at 24 h after cardioversion had pronounced atrial dysfunction (i.e. considerably lower than the lower limit of the reference range), which made the diagnosis of atrial dysfunction evident. With improvement of atrial function over time, more single values were recorded closer to the lower limit of normal. At time of the recheck examination, several cases with a value below the lower reference range for active LA FAC, had very low-normal S_L and SR_L values. This must be taken into consideration when interpreting the results. Atrial S_L has very high sensitivity in identifying increased atrial stiffness and fibrosis, and therefore dysfunction, in man with AF [41]. Because of its accuracy to quantify myocardial deformation, it is suggested to be used in addition to conventional variables to aid in prognostication and follow-up of patients [21]. Because of the low sample size and the lack of a gold standard for the diagnosis of atrial dysfunction, no inference can be made whether S_L or SR_L have a higher or lower sensitivity to detect long-term atrial stunning compared to conventional variables in horses after successful treatment of AF. Lacking sufficiently accurate data regarding time in NSR after successful cardioversion, it was not the scope of this study to investigate the ability of S_L and SR_L to predict the recurrence of AF after conversion of AF to NSR. Therefore, we suggest using 2DST-derived S_L and SR_L complementary to conventional variables for the assessment of atrial dysfunction in horses. Future studies, including more cases with long-term follow-up, will need to define the prognostic value for S_L and SR_L to predict the risk of AF recurrence. The respective cutoff values for S_L and SR_L will certainly be different from the limits of the reference intervals that were used to define atrial dysfunction in this proof-of-concept study.

The results of this study indicate that 2DST measurements of atrial dysfunction and improvement of atrial function over time are not markedly influenced by treatment method. Horses in this study were either treated by means of TVEC (11 cases) or medically using QS (ten cases). Atrial dysfunction occurs with all modes of cardioversion, including spontaneous conversion, however, some studies in other species have demonstrated that electrical cardioversion causes prolonged and more severe LA dysfunction [42,43]. In this study, no significant difference in atrial dysfunction between treatment groups was identified at any time point for active LA FAC and S_L. However, there was a significant difference in the rate of atrial myocardial deformation at 72 h and the follow-up examination between treatment groups. Horses that were treated with QS had significantly higher SR_L (i.e. more negative) than horses treated with TVEC. However, treatment method was not randomized in this study but largely reflected the clinicians' preference. In general, QS treatment was more often used in patients with short duration AF, while TVEC was more often used in cases with long duration AF or in cases where previous QS treatment had failed [2,44–46]. In addition, the small number of horses and the inclusion of one horse with two AF recurrences as separate cases represent limitations regarding this result. Therefore, conclusions on the influence of treatment modality on the degree of atrial dysfunction and recovery thereof cannot be drawn. Left atrial size might influence atrial function. However, there was no significant difference of LA size between treatment groups at any time point that would have influenced this result. Overall, there was no significant change in LA size over time using three of four described measurements for LA size. Other studies in horses after successful AF cardioversion reported significant changes in several measurements of LA size within 7 weeks [6]. The discrepancy of those results might be explained by differences in study samples, the shorter long-term follow-up period used in this study, and the fact that more than half of the cases already had normal LA size 24 h after cardioversion.

In the present study, HR during echocardiography was considered normal. No differences were detected between treatment groups while HR decreased slightly with increasing time after treatment. Recently, we showed that mildly elevated HR up to 50 beats per minute did not have a recognizable effect on the feasibility of 2DST analyses, whereas HR was positively correlated with S_L and SR_L during atrial active contraction phase [20]. Hence, the slight decrease in HR over time might have counteracted, to a small degree, the increases in S_L and SR_L observed in this study.

Besides the intrinsic limitations of speckle tracking echocardiography as described previously [20], this study has further limitations. One limitation is that 2DST analyses were not performed before cardioversion, which might be useful for prognostication of success of cardioversion and AF recurrence as demonstrated in people [21]. The limiting factor was that 2DST in horses was established using a P wave trigger rather than a R wave trigger to define the onset of S_L and SR_L [20]. While the P wave trigger is physiologically more appropriate to quantify atrial contractile function and is recommended to be given priority over the R wave trigger method for patients in sinus rhythm [47], analyses using the P wave trigger cannot be performed in patients with AF.

A second limitation is that the number of cases included in this study was small and that cases in the treatment groups were not matched regarding age, BWT and sex. Further limitations include that measurements were not performed blinded to time of examination or horse identity and that the influence of duration of AF, the number and total energy of electrical shocks, the total dose of QS and underlying structural diseases were not taken into consideration. Sotalol and quinapril were administered to some horses after cardioversion. Owing to the small sample size, the potential effect of this supplementary medication on atrial mechanical function was not investigated. However, because this was a proof-of-concept study for the use of 2DST for detection of LA mechanical dysfunction, the influence of additional drug treatment on LA mechanical function was not a primary research question.

Echocardiographic images were obtained using two different ultrasound systems, a GE Vivid 7 echocardiograph with a M4S probe and a GE Vivid e95 echocardiograph with a 4Vc-D probe, with the Vivid 7 used primarily for QS cases. While newer generation ultrasound systems were shown to produce better quality images than older systems [48], information regarding the potential impact of ultrasound systems on speckle tracking analyses is scarce. One study comparing two different ultrasound systems and speckle tracking software by different manufactures found comparable results for assessment of ventricular myocardial function, with global longitudinal strain being the most robust parameter [49]. However, no data are available regarding different generations of ultrasound systems of the same manufacturer. In this study, every effort was made to obtain high quality, standardized images at appropriate frame rates regardless of ultrasound system used. Subjectively, 2D image quality did not differ to a marked extent. Most importantly, all 2DST analyses were performed batchwise for the purpose of this study using the same EchoPAC software[b] version, therefore excluding possible influence of varying 2DST algorithms.

Conclusions

In conclusion, the results of this study provide proof-of-concept for using 2DST-derived global S_L and SR_L to diagnose atrial contractile dysfunction in horses with AF after successful cardioversion to NSR. To investigate the clinical value of 2DST variables to predict AF recurrence and identify the variables with the highest prognostic value, larger studies with long-term follow-up of all cases are necessary.

Conflict of interest statement

The authors do not have any conflicts of interest Q1 to disclose.

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